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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Applicati n No. | Applicant(s) | |
|---|---|---|---|
| | 09/808,382 | REUBINOFF ET AL. | |
| | Examiner | Art Unit | |
| | Thái-An N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-85* is/are pending in the application.

4a) Of the above claim(s) *1-7,28-38 and 69-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-27, 39-50, 52-55, 57-59, 64-68* is/are rejected.

7)☒ Claim(s) *51,56 and 60-63* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants' Amendment, filed 7/11/03, Paper No. 13, has been entered. Claims 8, 11, 14, 20, 23, 27, 39-46, 50, 58 and 64 have been amended.

Claims 1-85 are pending. Claims 8-27 and 39-68 are under current examination. Claims 1-7, 28-38 and 69-85 are withdrawn from consideration.

Any rejection made of record in the prior Office action, mailed 1/16/03, Paper No. 10, and not made of record in the instant Office action, has been withdrawn in view of Applicants' arguments and/or amendments to the claims.

### *Election/Restrictions*

This application contains claims 1-7, 28-38 and 69-85 that are drawn to an invention nonelected with traverse in Paper No. 9. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claims 1-7, 28-38 and 69-85 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group(s), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Drawings*

Applicants' Drawings, filed 7/22/03, have been entered and are approved by the Examiner.

### *Claim Objections*

Claims 51, 56 and 60-63 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claim 14 is maintained under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 10-12 of the prior Office action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 14 is directed to a neural progenitor cell wherein the cell is capable of transdifferentiation into other progenitor cell lineages to generate stem cells and differentiated cells of non-neural phenotype.

Applicants argue that an embodiment of the instant invention is directed to ES cell-derived neural progenitor cells [NPCs]. Applicants argue that the NPCs of the instant invention are distinct from neural stem cells [NSCs] and are different products, that there are significant differences between the two cell types, with regard to the stage of development that each originates from and their developmental potential. Applicants submit that human ES cell [hES]-derived NPCs originate from the earliest stage of development of the neural system, which is the neuroectoderm. In contrast, NSCs originate from specific regions in the fetal and adult brains and are formed at yet an undetermined stage of brain development but at a later stage than the neuroectoderm stage of embryonic development. Applicants argue that neural progenitors are derived from the very first stage of differentiation of hES cell colonies, where NPCs are derived from early progenitor

cells that do not express neural markers, but are destined to differentiate into neural progenitors in the appropriate culture conditions. The early progenitors do not express markers of undifferentiated ES cells or the earliest neuroectodermal marker N-CAM. Applicants cite Reubinoff *et al.* See p. 18 of the Response.

Applicants submit that a marker is not a proper characteristic to distinguish between NPCs and NSCs. See p. 19, 2nd ¶. Applicants provide Uchida *et al.*, wherein the authors derived human NSCs by sorting and selecting cells expressing the cell surface marker AC133, which is a marker of hematopoietic stem cells. Applicants argue that the AC133 stem cells of Uchida have been isolated from human brains but are not hematopoietic stem cells, although they express the same markers as hematopoietic stem cells. Applicants argue that the AC133 stem cells of Uchida are characterized physically differently from hematopoietic stem cells mainly by their developmental potential, *i.e.,* their ability to differentiate and give rise to neural cells. See p. 19 of the Response.

Applicants state that even though hES cell-derived NPCs may share the expression of similar markers with the NSCs, this does not mean that NPCs are the same as NSCs. Applicants argue that it is known in the art that stem cells in general share the expression of some markers and genes, thus, it is not surprising that these two cell types [NPCs and NSCs] share certain similar markers. Applicants state that NPCs and NSCs have not been systemically compared and that a marker that will differentiate between the two cell types has not yet been

found. Applicants argue that the way to distinguish NSCs and NPCs at present is to consider parameters such as developmental potential and gene expression profiles, and not their marker expression. Applicants argue that NPCs and NSCs differ in both developmental potential and gene expression and that NPCs have a pbroader developmental potential when compared to NSCs. NPCs can be differentiated *in vitro* into various neural cells and provide Kim and Brustle as evidence. Applicants submit that the inventors have shown that the NPCs of the instant invention have been shown to express the key regulatory genes along specific differentiation pathways [Exhibit 2] and that while NSCs can give rise to the three major cell types of the CNS, their capability to express key genes along differentiation pathways *in vivo* or to respond to signal molecules that direct differentiation during normal development has not been demonstrated. See pp. 19-20 of the Response.

Applicants provide Exhibit 1 show that the NPCs do not express markers of undifferentiated ES cells or the earliest neuroectodermal marker N-CAM, Exhibit 2 to show that human ES-express key regulatory genes along specific differentiation pathways and Exhibit 3 to provide evidence that the developmental potential of human ES cell derived neural progenitors is altered along their propagation. Applicants conclude that these three exhibits provide evidence as to how the NPCs of the instant invention differ from NSCs. This is not found to be persuasive. Firstly, Applicants provide no evidence of record to show that NPCs have a, "more

potent developmental potential." None of the exhibits provided by Applicant compare NPCs to NSCs to demonstrate differences between the two cell types. Furthermore, these exhibits are not found to be persuasive as they represent uncorroborated evidence and further, it is unclear the source of these exhibits.

Applicants argue that it has been demonstrated by the inventors and others in the art that the early neural progenitor cells can also be directed to differentiate into insulin producing cells and that this result confirms the belief that NPCs do in fact have a more developmental potential. Applicants argue that while NSCs and NPCs may share the expression of certain makers and can be both propagated in vitro and give rise to the three neural cell lineages, NPCs are more primitive precursors of the nervous system and have a broader developmental potential when compared to NSCs, and thus, NPCs and NSCs are different products. See p. 21 of the Response.

Applicants arguments have been considered, however, they are not found to be persuasive. Applicants argue that the cells of the instant invention have been shown to be able to differentiate into insulin producing cells. However, Applicants have failed to produce evidence or teachings of record to support this argument. MPEP §716.01(c) states:

> *The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements*

> *regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.*

The references of Reubinoff [Exhibit 4], Uchida [Exhibit 6], and Kim [Exhibit 5] have been considered. These references have been provided to show that NPCs of the instant invention are different products from NSCs known in the art. The enablement rejection is not directed to differences between NPCs and NSCs, but to the ability of the NPCs of the instant invention to *transdifferentiate*.

Applicants argue that the specification teaches transdifferentiation of neural progenitors and point to p. 45 of the specification as evidence that specification teaches that neural progenitors can transdifferentiate into mesodermal cells such as hemangioblast cells. Applicants further note that the references cited in the prior Office action [Kennea *et al*] are premised on co-culturing experiments involving NSCs or other adult stem cells and human ES cells. These experiments indicated that the resulting de-differentiated [transdifferentiated] cells were possibly NSC/ES cell hybrids. Applicants argue that the instant invention is directed to NPCs, not NSCs, and that the NPCs are not co-cultured with human ES cells. Furthermore, Applicants argue that NPCs have been confirmed to possess a much broader differentiation potential than NSCs. As such, Applicants conclude that transdifferentiation is enabled. See pp. 22-23 of the Response.

Applicants' arguments have been carefully considered, but are not found to be persuasive. The specification, as cited by the Applicant, merely states that expression of mesodermal markers such as flk-1 and CD-34 has been demonstrated in the NPCs of the instant invention, and that this may 1) indicate the presence of mesodermal primitive cells or 2) that the primitive neural progenitors within the spheres express these mesodermal markers. See p. 45, lines 25-30. Furthermore, the specification states that, "The expression of the markers may indicate the possible high plasticity of the neural progenitors to transdifferentiate into mesodermal cells." This is unpersuasive. The instant specification fails to enable the claimed invention because it fails to teach or provide evidence to show that the NPCs of the instant invention are, in any way, transdifferentiated. Clearly, as stated by Applicant, the mere expression of marker is not a definitive way distinguish one cell type from another, as many cells may express the same marker. Furthermore, the specification does not teach that the NPCs are capable of transdifferentiation, the specification fails to show or characterize the types of cells which were shown to express flk-1 and CD-34, and that the specification only speculates as to why the NPCs of the instant invention express flk-1 and CD-34. The specification fails to show that the NPCs are truly mesodermal cells [as contemplated]; that they function as mesodermal cells. Note that the claims require that the cell transdifferentiate to "other progenitor cell lineages to generate stem cells and differentiated cells of non-neural phenotype." The specification fails to

show that the NPC cells that express flk-1 and CD-34 are stem cells or differentiated cells of a non-neural phenotype, and further, the specification fails to characterize the cells with particularity to show that they are, for example, mesodermal cells.

With regard to Applicants' arguments that the cited art of Kennea is not relevant to the instant invention, in particular, because the NPCs of the present invention are not co-cultured with human ES cells is not found persuasive. Kennea *et al.* is provided as evidence to show that the state of the art of transdifferentiation is both unpredictable and undeveloped. Although the particular methodology of Kennea is not identical to that of the specification, it is clearly taught that the concept of transdifferentiation is unpredictable and undeveloped, and that the various mechanisms that underlie the process have yet to be characterized. The specification fails to provide teachings or evidence to overcome these unpredictabilities. The specification fails to show that the cells of the instant invention are transdifferentiated into progenitor cell lineages to generate stem cells or differentiated cells of non-neural phenotype. The specification fails to teach how to reprogram the cells of the instant invention such that one of skill in the art would be able to reprogram the NPCs of the instant invention.

As such, with respect to the unpredictable nature of transdifferentiation of neural progenitor cells, and particularly when taken with the specification's lack of teachings or sufficient to show that the claimed neural progenitor cells could

transdifferentiate into cell lineages which would generate stem cells and/or differentiated cells of a non-neural phenotype, it would not be predictable that the progenitor cells of the instant invention would transdifferentiate into cell lineages which would generate stem cells and/or differentiated cells of a non-neural phenotype.

Accordingly, the unpredictable and undeveloped state of the art of transdifferentiation of neural progenitor cells, and as well as the lack of guidance or teachings, or working examples provided by the specification to show that the described neural progenitor cells could transdifferentiate into other cell lineages to generate stem cells and differentiated cells of non-neural phenotypes, it would have required undue experimentation for one skilled in the art to use the claimed methods.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claim 39 is maintained. The claim recites a method of "somatic differentiation of stem cells" in line 1 of the claim. It is unclear what "somatic differentiation" encompasses. Applicatns point to the specification for definition and support of this term. The specification merely states that somatic differentiation may be induce *in vitro*. However, the specification fails to provide a

definition for what somatic differentiation is. For example, are the cells only capable of differentiating into somatic cells? If so, what conditions would provide for such controlled differentiation? Claims 40-49 depend from claim 39.

*Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The prior rejection of claims 8-13, 15-27, 47-50, 52-54 and 58 under 35 U.S.C. 102(b) as being anticipated by Flax *et al.* [**Nat. Biotech** (1998) 16:1033-1039] is maintained for reasons of record advance on pages 15-19 of the prior Office action.

Applicants argue that the claims of the instant invention are directed to human neural progenitor cell lines derived from undifferentiated human ES [NPCs] in vitro. Applicants argue that the NPCs of the instant invention are different from the NSCs of Flax, which were isolated from human fetal telecephalon. Applicants further argue that NPCs and NSCs are physically different from each other, with respect to gene expression profiles and developmental potential. As such, the cells

of the claimed invention are a different product from what is claimed in the present invention. See p. 28 of the Response.

Applicants' arguments are not found to be persuasive. The claims require a differentiated committed human progenitor cell line capable of differentiation and propogation into mature neurons or glial cells, wherein the cell line is derived from undifferentiated pluripotent human embryonic stem cells *in vitro*. Applicants have not provided evidence of record to show that the NPCs of the instant invention are different products than NSCs taught by Flax. For example, Applicants argue that NPCs are derived from early progenitor cells that "are not expression neural markers but are destined to differentiate into neural progenitors in the appropriate culture conditions." See p. 18, 3rd ¶ of the Response. The claims merely require that the cells are capable of differentiation and propagation into mature neurons or glial cells. Flax teach NSCs which are capable of differentiation into neurons and oligodendrocytes. Applicants argue that although the NPCs of the instant invention may share the expression of certain similar markers with NSCs, "this fact *per se* does not mean that the NPCs are the same as NSCs." Applicants further submit that NPCs and NSCs have not been systematically compared. See line 1 of p. 20 of the Response. As Applicants have submitted that NPCs and NSCs have not been systematically compared, it is unclear how differences between two cell types can be distinguished. Furthermore, Applicants argue that the way to distinguish between NPCs and NSCs is by developmental potential and gene expression profiles, not

their marker expressions. Applicants submit that the NPCs of the instant invention express the key regulatory genes along specific differentiation pathways *in vivo* [Exhibit 2] and that the NPCs of the instant invention have been directed to differentiate into insulin producing cells. See p. 21, 2nd ¶ of the Response. Applicants have not provided evidence of record to show that the NPCs of the instant invention are capable of differentiation into insulin producing cells. Furthermore, it is reiterated that the claims, as broadly written, do not require a broader, more potent developmental potential or the expression [or lack thereof] or particular genes.

With regard to the limitation that the cell line is "derived from undifferentiated pluripotent human ES cells *in* vitro," it is reiterated that all cells are derived from ES cells, and that the requirement that the differentiation take place *in vitro* renders the claim a product-by-process claim. See *supra.*

Accordingly, Flax anticipate the claimed invention.

The prior rejection of claims 39-49 under 35 U.S.C. 102(b) as being anticipated by Thomson [**US Pat No. 5,843,780**, published December 1, 1998] is *withdrawn* in view of Applicants' amendments to the claims reciting "human pluripotent".

Claims 39-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Shamblott *et al.* [**PNAS**, 95:13726-13731, cited on Applicants' Information Disclosure Statement, Filed 7/02/01, Paper No. 3].

The claims are directed to methods of inducing somatic differentiation of stem cells *in vitro* into progenitor cells by obtaining undifferentiated human pluripotent ES cells and providing a controlled differentiating condition which is non-permissive for stem-cell renewal, does not kill cells or induces unidirectional differentiation toward extraembryonic lineages.

Claims 44 and 45 recite undifferentiated ES cells prepared by the method of by a specific method. Thus, the ES cells recited in these claims are product-by-process claims [see *supra*]. Note that with regard to claims 40 and 41, which discuss the expression of various undifferentiated embryonic stem cell markers, these markers are inherent properties of undifferentiated ES cells. That is, that, "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

Shamblott teach the generation of pluripotent human ES cells from cultured human primordial germ cells. Gonadal ridges from post-fertilization human embryos were collected and the cells cultured. The cells were then analyzed by

detection of AP activity and immunohistochemistry. See Materials and Methods. The cells were found to test positive for five immunological markers of ES cells [SSEA-1, SSEA-3, SSEA-4, TRA-1-60 and TRA-1-81], see Abstract. The immunohistochemical analysis of embryoid bodies revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers. See Abstract. Particularly, the immunohistochemical analysis of the embryoid bodies found ectodermal derivatives of cells suggestive of neuroepithelia and antineurofilament cells. See p. 13729, 2nd column, 1st full ¶. Shamblott teach that the cells are pluripotent stem cells that are positive for markers commonly used to identify pluripotent stem cells, have morphology similar to mouse ES and EG cells, maintain a normal and stable karyotype, and can be differentiated into a wide variety of cell types. See p. 13729, 2nd column, Discussion.

Applicants argue that claim 39, as amended requires "controlled" differentiation, and that "uncontrolled" differentiation is an all-or none phenomenon wherein the supporting feeder layer is removed or when the cells, upon reaching confluence, are allowed to "over-grow". This is not found to be persuasive. The claim merely requires "a controlled differentiating signal". This, as broadly claimed, merely requires that differentiation is occurs under a particular condition. Clearly, the differentiation conditions as taught would not kill cells, and as such fulfills the limitations of the claims. Indeed, claim 46 states that culturing undifferentiated cells at a high density for prolonged periods, or, for example

culturing the cells in serum free media is sufficient for inducing somatic differentiation. As such, the conditions taught by Shamblott would be considered a "controlled differentiating" signal with regard to the claimed invention.

Applicants further argue that claim 39, as amended requires "non-permissive" conditions for stem cell renewal. It is noted that the cells, once differentiated, do not renew stem cells. Furthermore, as noted above, claim 46 provides various conditions for inducing somatic differentiation, which are clearly anticipated by Shamblott.

Accordingly, Shamblott anticipate the claimed invention.

The prior rejection of claims 8-13, 15-27, 50-54 and 58 under 35 U.S.C. 102(b) as being anticipated by Vescovi *et al.* [**Exp. Neurol** (March 1999) 156:71-83] is *maintained* for reasons of record.

Applicants argue that Vescovi teach NSCs, whereas the claimed invention is directed to NPCs. Applicants argue that, prior to the present invention, one could grow NSCs using established methods as taught by Vescovi, however, no one could successfully culture human ES cells as presently claimed. Applicants argue that the present invention teaches human ES cells, human ES cell derived NPCs and not NSCs, and a method of culturing and differentiating the human ES cells into progenitor cells under controlled conditions. See pp. 30-31 of Applicants' Response.

Applicants' arguments have been considered but are not found to be persuasive. The human neural embryonic stem cells, as taught by Vescovi anticipate the claimed invention because the claimed invention recites no limitations that distinguish Applicants' NPCs from known NSCs. Applicants have not provided evidence of record to show that the NPCs of the instant invention are different products than NSCs taught by Vescovi. For example, Applicants argue that NPCs are derived from early progenitor cells that "are not expression neural markers but are destined to differentiate into neural progenitors in the appropriate culture conditions." See p. 18, 3rd ¶ of the Response. The claims merely require that the cells are capable of differentiation and propagation into mature neurons or glial cells. Vescovi teach the generation of neurons and glia after implantation of the NSCs into rat brains. Applicants argue that although the NPCs of the instant invention may share the expression of certain similar markers with NSCs, "this fact *per se* does not mean that the NPCs are the same as NSCs." Applicants further submit that NPCs and NSCs have not been systematically compared. See line 1 of p. 20 of the Response. As Applicants have submitted that NPCs and NSCs have not been systematically compared, it is unclear how differences between two cell types can be distinguished. Furthermore, Applicants argue that the way to distinguish between NPCs and NSCs is by developmental potential and gene expression profiles, not their marker expressions. Applicants submit that the NPCs of the instant invention express the key regulatory genes along specific differentiation

pathways *in vivo* [Exhibit 2] and that the NPCs of the instant invention have been directed to differentiate into insulin producing cells. See p. 21, 2nd ¶ of the Response. Applicants have not provided evidence of record to show that the NPCs of the instant invention are capable of differentiation into insulin producing cells. Furthermore, it is reiterated that the claims, as broadly written, do not require a broader, more potent developmental potential or the expression [or lack thereof] or particular genes.

Accordingly, Vescovi anticipate the claimed invention.

The prior rejection of claims 8, 10-13, 15, 16, 23-25, 50, 52-55, 58 and 59 under 35 U.S.C. 102(b) as being anticipated by Anderson *et al.* [U.S. Pat. No. 5,693,482, published December 2, 1997] is *maintained* for reasons of record.

Applicants argue that Anderson teach rat multipotent NSCs and methods of isolating such cells and that the instant invention is directed to human NPCs and methods for propagation and differentiation of such cells. As such, Applicants argue that Anderson do not anticipate the claimed invention. See p. 31 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. Anderson teach multipotent neural stem cells illustrated by rat neural stem cells, but they state that neural stem cells can also be isolated from humans [see col. 6, lines 49-53]. They further teach methods of culturing the neural stem cells. As such, Anderson teaches the limitations of the claims.

Accordingly, Anderson anticipate the claimed invention.

The prior rejection of claims 8, 11-13, 15, 16, 23-25, 50-54 and 58 under 35 U.S.C. 102(a) as being anticipated by Johansson *et al.* [**Exp. Cell Res.** (Dec. 1999) 253:733-736] is *maintained* for reasons of record.

Applicants argue that Johansson teach *bona fide* NSCs and the process of obtaining and culturing such cells. Applicants argue that in contrast, the product of making the product recited in the claims are directed to neural progenitor cells derived from undifferentiated human ES cells *in vitro* and the process of making thereof. The NSCs are usually derived from neural tissue, either embryonic fetal or adult, while ES cells are derived from an inner cell mass of a blastocyst and have the potential to differentiate into any cell lineage. Applicants further argue that NSCs and NPCs are two totally different products. See pp. 31-32 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. The claims recite products and methods of using such products that do not distinguish the claims from the prior art. In particular, Applicants have not provided evidence of record to show how NPCs of the instant invention are different from the NSCs taught in the art. See *supra.* Furthermore, the claims as broadly written do not require that the NPC cells of the invention be derived from neural tissues, for example.

Accordingly, Johansson teach the claimed invention.

*Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The prior rejection of claims 64-68 under 35 U.S.C. 103(a) as being unpatentable over Thomson [**US Pat No. 5,843,780**, published December 1, 1998] when taken with Johansson *et al.* [**Exp. Cell Res.** (Dec. 1999) 253:733-736] maintained for reasons of record.

Applicants argue that the methods of claims 64-68 are directed to methods of producing an enriched preparation of human ES cell derived neural progenitor cells, and that the undifferentiated human ES cells in the present invention are induced under controlled conditions to differentiated into neural progenitor cells. Applicants note that Thomson merely teaches the isolation of primate ES cells, which spontaneously differentiate when culturing in high density and that nowhere does Thomson teach or suggest that human ES cells are induced to differentiate into neural progenitor cells under controlled conditions, such as removing growth factors. Applicants further note that Johansson merely teach bona fide neural stem cells and the process of obtaining and culturing such cells. Applicants argue that the suggestion to use the claimed method to make an enriched preparation of human ES cell derived neural progenitor cells appears nowhere in the cited combination of Thomson and Johansson. See pp. 32-33 of the Response.

Applicants' arguments have been considered, but are not found to be persuasive. Thomson clearly teach the isolation of primate ES cells, and in particular discuss the isolation of human ES cells using the techniques. See col. 7, lines 1-5. Furthermore, with regard to limitations such as "controlled differentiation", the claims merely require that the cells are cultured under conditions which are non-permissive for stem cell renewal, does not kill cells or induces unidirectional differentiation toward extraembryonic lineages. Thomson clearly fulfills these limitations because the cells that are differentiated to not de-

differentiation nor are they killed. Furthermore, it is reiterate that, as Applicants have not provided any teachings or evidence of record to show the differences between the NPCs of the claimed invention and NSCs taught in the art, the claimed invention is rendered obvious. With regard to the suggestion to use the claimed method to make an enriched population of neural progenitor cells, it would be obvious to culture the cells which produced neural stem cells, as taught by Thomson, under culture conditions as taught by Johansson because such culture conditions would provide methods to maintains and propagate neural stem cells and it was an art-recognized goal to optimize culturing conditions for stem cells.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

The prior rejection of claim 56 under 35 U.S.C. 103(a) as being unpatentable over Anderson [**U.S. Pat. No. 5,693,482**, published December 2, 1997] is *withdrawn.*

The prior rejection of claim 57 under 35 U.S.C. 103(a) as being unpatentable over Anderson [**U.S. Pat. No. 5,693,482**, published December 2, 1997] when taken with van Inzen *et al.* [**Biochimica et Biophys Acta** (1996) 1312:21-26] is *withdrawn* in view of Applicants' arguments and/or amendment(s).

*Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

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